Assessment of lung ultrasound B-lines in dogs with different stages of chronic valvular heart disease

Vezzosi, T ; Mannucci, T ; Pistoresi, A ; Toma, F ; Tognetti, R ; Zini, E ; Domenech, O ; Auriemma, E ; Citi, S

Abstract: BACKGROUND: In dogs with chronic valvular heart disease (CVHD), early recognition of pulmonary edema (PE) is of paramount importance. Recent studies in dogs showed that lung ultrasound examination (LUS) is a useful technique to diagnose cardiogenic PE. OBJECTIVES: To describe LUS features in dogs with different stages of CVHD, and to determine its diagnostic accuracy in detecting PE using thoracic radiography as the reference standard. ANIMALS: Sixty-three dogs with CVHD. METHODS: Prospective, multicenter, cross-sectional study. Each dog underwent physical examination, echocardiography, thoracic radiography, and LUS. The LUS findings were classified as absent, rare, numerous, or confluent B-lines. Sensitivity, specificity, and positive and negative predictive values of LUS B-lines to identify PE were calculated using thoracic radiography as the reference standard. RESULTS: Dogs in stage B1 had absent or rare B-lines in 14 of 15 cases (93.3%). Dogs in stage B2 had absent or rare B-lines in 16 of 18 cases (88.9%). All dogs in stage C, without radiographic signs of PE, had absent or rare B-lines. Dogs in stage C, with radiographic signs of PE, had numerous or confluent B-lines in 18 of 20 cases (90%). Lung ultrasound examination detected PE with a sensitivity of 90%, specificity of 93%, and with positive and negative predictive values of 85.7 and 95.2%, respectively. CONCLUSIONS AND CLINICAL IMPORTANCE: Lung ultrasound examination showed good diagnostic accuracy to identify cardiogenic PE and might be helpful in staging dogs with CVHD. Lung ultrasound examination should be considered as a new, noninvasive diagnostic tool for clinicians managing CVHD in dogs.

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Assessment of lung ultrasound B-lines in dogs with different stages of chronic valvular heart disease

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Running title: lung ultrasound in mitral valve disease

Keywords: heart failure, pulmonary edema, thoracic ultrasonography, lung comets.

Abbreviations:

CHF	congestive heart failure
CVHD	chronic valvular heart disease
E/A	E wave to A wave ratio of transmitral flow
Emax	peak velocity of E wave of transmitral flow
LA/Ao	left atrium aortic root ratio

LUS	lung ultrasound
LVIDDn	normalized left ventricular internal diameter in diastole
PE	pulmonary edema

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Abstract

Background: In dogs with chronic valvular heart disease (CVHD), early recognition of pulmonary edema (PE) is of paramount importance. Recent studies in dogs showed that lung ultrasound (LUS) is a good technique to diagnose cardiogenic PE.

Objectives: To describe LUS features in dogs with different stages of CVHD, and to determine its diagnostic accuracy in detecting PE using thoracic radiography as reference method.

Animals: Sixty-three dogs with CVHD.

Methods: Prospective, multicenter, cross-sectional study. Each dog underwent physical examination, echocardiography, thoracic radiography and LUS. The LUS findings were classified in absent, rare, numerous or confluent B-lines. Sensitivity, specificity, positive and negative predictive values of LUS B-lines to identify PE were calculated using thoracic radiography set as reference.

Results: Dogs in stage B1 had absent or rare B-lines in 14 out of 15 cases (93.3%). Dogs in stage B2 presented absent or rare B-lines in 16 out of 18 cases (88.9%). All dogs in stage C, without radiographic signs of PE, presented absent or rare B-lines. Dogs in stage C, with radiographic signs of PE, showed numerous or confluent B-lines in 18 out of 20 cases (90%). Lung ultrasound detected PE with a sensitivity of 90%, specificity of 93%, positive and negative predictive value of 85.7% and 95.2%, respectively.

Conclusions and Clinical Importance: Lung ultrasound shows good diagnostic accuracy to identify cardiogenic PE and might be helpful in staging dogs with CVHD. Lung ultrasound should be considered as a new, non-invasive diagnostic tool for

clinicians during the management of CVHD in dogs.

Introduction

Chronic valvular heart disease (CVHD) is the most common acquired cardiac disease in dogs.[1] The disease is characterized by a progressive degeneration of the mitral valve, which leads to mitral regurgitation. Mitral regurgitation can lead to cardiac remodelling and the development of congestive heart failure (CHF). Although most dogs with CVHD remain asymptomatic for years, approximately one third develop CHF and die from this heart disease.[2] Thus, both early recognition and prompt treatment of cardiac remodelling and CHF are of utmost clinical importance.[3-5] Thoracic radiography is the most commonly used method for the diagnosis of cardiogenic pulmonary edema (PE) and is currently considered the standard technique for diagnosis of PE in dogs.[6,7]

In people, lung ultrasound (LUS) is used in the diagnosis of acute respiratory failure both in emergency medicine and cardiology.[8-10] In people with acute heart failure, LUS is used to assess and stage PE with reliable results.[11-13] In patients with PE, ultrasound reveals artefacts that appear as vertical hyperechoic lines with a narrow base that emerge from the surface of the pleura, extending to the distal edge of the screen, which are defined as B-lines.[14-16] These B-lines correspond to the thickening of the subpleural and interlobular septum or to the presence of extravascular fluids in the lungs.[12,14] Studies in people have demonstrated that the number and distribution of B-lines correlate with pulmonary capillary wedge pressure, the presence of extravascular fluid in lungs, and the severity of clinical presentation and prognosis.[15,17-19] Some patients with interstitial PE present B-lines prior to the onset of clinical or radiographic signs associated with heart failure; LUS may be of clinical utility in the early diagnosis of PE in these cases.[17]

In veterinary medicine, LUS was initially used in horses to evaluate recurrent airway obstruction, exercise-induced pulmonary haemorrhage, pulmonary fibrosis, and interstitial pneumonia.[20] Recent studies in dogs have demonstrated that LUS may be a viable technique to aid in the diagnosis of cardiogenic PE.[21-23] However, based on current literature, no studies have described LUS findings in dogs with pre-clinical CVHD versus dogs in CHF.

The aims of the present study were to describe LUS features in dogs with different stages of CVHD in accordance to the ACVIM consensus classification system and to determine the diagnostic accuracy of LUS to detect PE using thoracic radiography as the reference method.

Materials and methods

The study protocol and informed consent were reviewed and approved by the Institutional Welfare and Ethics Committee of the University of Pisa (permission number 33472/2016).

Dogs were prospectively recruited from August 2015 to September 2016 at the Department of Veterinary Sciences of the University of Pisa and the Department of Cardiology of the Istituto Veterinario di Novara. Each dog underwent a physical examination, echocardiography, thoracic radiography and LUS examination.

Inclusion criteria were the presence of a typical heart murmur and an echocardiographic diagnosis of CVHD, characterized by degenerative changes in the mitral valve leaflets, mitral valve prolapse, and the presence of systolic mitral regurgitant flow.[24]

Collected echocardiographic data were normalized left ventricular internal diameter in diastole (LVIDDn), left atrial to aortic root ratio (LA/Ao) and flow data including peak velocity of E wave of transmitral flow (Emax) and E wave to A wave ratio of transmitral flow (E/A ratio).

Dogs with CVHD were classified into stages B1, B2, C and D according to the ACVIM classification.[6] Stage B was defined as subclinical heart disease without (B1) or with (B2) evidence of left cardiomegaly, defined as LA/Ao ≥ 1.6,[25] LVIDDn > 1.73,[26] or both. Dogs belonged to stage C if they presented a history or current clinical signs of CHF in conjunction with past or current evidence of PE on thoracic radiographs. Finally, dogs with past or current evidence of PE on thoracic radiographs that had been treated and relapsed or failed to respond to the initial treatment were classified as stage D.[6]

Dogs with pleural effusion were excluded from the study. Moreover, dogs with another concomitant heart disease, in addition to CVHD, were excluded.

Evaluation of latero-lateral and orthogonal (ventrodorsal or dorsoventral) radiographic views of the thorax were performed. A board-certified radiologist (E.A) and a skilled radiologist (S.C) reviewed the images independently. All studies were randomly ordered and radiologists were blinded to the animal’s history, examination date, initial radiological interpretation and echocardiographic diagnosis, as well as LUS findings. After interpretation of films, results of the 2 readers were compared. If there was disagreement with regard to the presence or absence of CHF, any discrepancy was resolved by consensus. Radiographic patterns of PE were classified according to location as follows: diffuse, when all the lung fields were involved; perihilar, when only the region surrounding the lung hilum was involved; focal, when a single area of one or more lung lobes was involved.[27]

Each dog underwent a LUS examination on the same day as the echocardiography and thoracic radiographs. Two sonographers (T.M., E.A.) performed the LUS studies using linear probes[a,b] with 2 different ultrasound machines.[c,d] To avoid lung atelectasis due to recumbency dogs were in quadrupedal posture and manually restrained. Hair was not clipped, alcohol and gel were used as coupling agents. Each hemithorax was examined by sliding the probe from dorsal to ventral, examining all the intercostal spaces. Following a previous study,[22] the presence of B-lines was evaluated as follows: absent (no B-lines for hemithorax); rare (≤ 3 B-lines for hemithorax); numerous (> 3 B-lines for hemithorax); and confluent (multiple B-lines blended together) (Figure 1). When we detected different LUS findings between the 2 hemithoraxes, the worst finding was assigned.

Statistical analysis

The normality of data distribution was tested using the Shapiro-Wilk test. Descriptive statistics were generated. A value of $P < 0.05$ was considered statistically significant. Differences in continuous data among dogs with different stages of CVHD (B1, B2 and C) was determined by one-way analysis of variance with subsequent comparisons using Tukey's multiple comparisons test (for normally distributed data) or by the Kruskal-Wallis test with subsequent comparisons using the Dunn test (for non-normally distributed data). For categorical variables, comparison between different stages of CVHD was performed with Fisher's exact tests.

To test the diagnostic accuracy of LUS in the detection of PE, dogs were divided into the following 2 groups: absent/rare B-lines versus numerous/confluent B-lines.[8,13,22,23,28] The sensitivity, specificity, positive and negative predictive values of LUS to detect PE were calculated using thoracic radiography as the reference standard.

For the statistical analyses, commercial software (GraphPadPrism 5) was used.

Results

The study included 63 dogs with a diagnosis of CVHD: 15 dogs in ACVIM stage B1, 18 dogs in ACVIM stage B2, and 30 dogs in ACVIM stage C. A total of 20 out of 30 dogs in ACVIM stage C (66.7%) presented radiographic signs of PE. In dogs with PE, 14 out of 20 (70%) presented a radiographic pattern of focal location, 3 out of 20 (15%) a diffuse location and 3 out of 20 (15%) a perihilar location. Baseline clinical characteristics of the dogs are presented in Table 1. There were no statistically significant differences between groups in terms of sex, age and body weight.

Regarding echocardiographic data, dogs in stage C had a significantly higher value of LA/Ao (median: 2.30, range: 1.75-3.68) in comparison with stage B2 (median: 1.80, range: 1.60-2.80) and stage B1 (median: 1.39, range: 1.00-1.50) ($P<0.0001$). Left atrial dimension in stage B2 was significantly greater than stage B1 ($P<0.05$). The peak E wave velocity of the diastolic transmitral flow was significantly higher in stage C (median: 1.51 m/s, range: 0.66, 2.30 m/s) in comparison to stage B2 (median: 0.98 m/s, range: 0.40-2.04 m/s) and stage B1 (median: 0.89 m/s, range: 0.66-1.02 m/s) (P=0.0007). Similarly, the E wave to A wave ratio of the transmitral flow was significantly higher only in stage C (median: 2.04, range: 0.67-4.20) in comparison to stage B2 (median: 1.10, range: 0.70-3.00) and B1 (median: 1.33, range: 0.75-1.65) (P<0.0001). Lastly, dogs in stage C had a higher value of LVIDDn (median: 2.21, range: 1.63-2.86) in comparison with stage B2 (median: 1.87, range: 1.39-2.34) and stage B1 (median: 1.48, range: 1.25-1.85) (P<0.0001). The LVIDDn in stage B2 was significantly greater than stage B1 (P<0.05).

The LUS findings in our sample are presented in Table 2. Dogs in stage B1 had absent or rare B-lines in 93.3% of cases (14/15); more specifically, 73.3% (11/15) presented absent B-lines and 20% (3/15) presented rare B-lines. Only 6.7% of dogs in stage B1 (1/15) showed numerous B-lines. Dogs in stage B2 presented absent or rare B-lines in 88.9% of cases (16/18). Specifically, 66.7% of dogs in stage B2 (12/18) presented absent B-lines and 22.2% (4/18) presented rare B-lines. Only 11.1% of dogs in stage B2 (2/18) showed numerous B-lines. Similarly, all dogs in stage C (10/10), without radiographic signs of PE, presented absent or rare B-lines. Of the dogs in stage C without radiographic signs of PE, 60% (6/10) presented absent B-lines and 40% (4/10) presented rare B-lines. Dogs in stage C with radiographic signs of PE showed numerous or confluent B-lines 90% of cases (18/20), with 55% (11/20) showing numerous B-lines and 20% (7/20) showing confluent B-lines, only 10% (2/20) presented rare B-lines.

The lung ultrasound had a 90.0% sensitivity and 93.0% specificity in differentiating dogs with and without PE as assessed by thoracic radiography, with a positive predictive value of 85.7%, and a negative predictive value of 95.2% (Table 3).

Discussion

To the authors' knowledge, this is the first study describing LUS findings in dogs with different stages of CVHD in accordance to the ACVIM classification scheme. This study found that the majority of dogs in stages B1 and B2 presented absent or rare B-lines. Similarly, all dogs in stage C without radiographic signs of PE presented absent or rare B-lines. Conversely, the majority of dogs in stage C with radiographic signs of PE presented numerous or confluent B-lines. These results are in line with findings in human medicine where the number of B-lines increases with a worsening of the heart failure class[9,29] and PE is diagnosed when numerous or confluent B-lines are detected.[8,9,18] Similarly, previous studies in dogs have shown that cardiogenic PE is associated with numerous or confluent B-lines on LUS. However, these studies only compared healthy dogs and dogs with radiographic signs of PE.[21-23]

In this study, LUS showed a good diagnostic accuracy in the detection of PE in dogs with CVHD, with a sensitivity of 90.0% and specificity of 93.0%. To the authors' knowledge, no previous studies have described the diagnostic accuracy of LUS in the detection of PE in dogs with different stages of CVHD. Our results are similar to findings in people where the sensitivity and specificity of LUS in detecting PE were 83-97% and 83-100%, respectively.[8,16,28,30,31]

In the present study, there were a few dogs in stage B1 (6.7%, 1/15) and B2 (11.1%, 2/18) showing numerous B-lines. A possible explanation might be the presence of an underlying pulmonary disease other than cardiogenic pulmonary edema that was not detected by conventional radiography. Presence of B-lines have been described in people and horses affected by pulmonary fibrosis, acute respiratory distress syndrome, pulmonary hemorrhages, pneumonia or lung cancer.[13,18,20,32] Another possible explanation for dogs with stage B1 and B2 with numerous B-lines might be the presence of mild cardiogenic pulmonary edema that was not detected by thoracic radiography. Although thoracic radiography is considered as the reference standard for the diagnosis of PE in clinical practice, there may be inter-reader variability.[7,33] Studies in humans have suggested that thoracic radiography can be less sensitive than LUS in revealing the presence of cardiogenic PE.[30]

Our study did not find 100% sensitivity of LUS for the detection of PE, similar to literature in people.[8,16,28-31] Two dogs in stage C with radiographic evidence of PE exhibited only rare B lines on LUS in the present series. In both cases, the pulmonary infiltrate was only perihilar. It is hypothesized that in patients with only perihilar edema, normo-ventilated peripheral lung tissue prevents B-lines from being shown, which would otherwise be visible if pathologic pulmonary parenchyma was present along the thoracic wall.

There are some limitations to the study that need to be addressed. The number of enrolled dogs was relatively small. However, the sample population of the study was homogeneous; indeed, only dogs with CVHD were included. It is assumed that a larger number of dogs would not provide dissimilar results. Moreover, intra- and inter-observer variability during the LUS acquisition was not evaluated. The evaluation of the number of B-lines might have been partially biased by the operator. However, many studies in people have demonstrated that intra- and inter-observer variability is clinically acceptable if the procedure is performed by trained operators.[34-36] A linear probe for the LUS examination was used in all dogs. However, there is currently no consensus in the veterinary literature regarding the best type of probe to be used for LUS.[21-23] It cannot be rule out that results of this study would have differed slightly using another type of probe, although linear high frequency probes are thought to provide the best resolution for scanning superficial structures. Lastly, in this study we used thoracic radiography as the reference method to evaluate pulmonary parenchyma. Computed tomography is a more sensitive and specific technique than thoracic radiography to diagnose cardiogenic pulmonary edema.[37] However, both in people and in dogs, thoracic radiography is the first line procedure to assess pulmonary congestion, and computed tomography is not a routine technique in heart failure, especially in acute PE.[1,6,37]

The findings of this study demonstrate that LUS has a good diagnostic accuracy to identify cardiogenic PE and that it might be useful in the staging of dogs with CVHD. Lung ultrasound is a new, quick and non-invasive diagnostic tool for the cardiologist, radiologist or intensive care specialist. It should be considered as complementary to thoracic radiography, and particularly useful when radiographic findings are unclear or in severely dyspneic dogs. In the future, it might be interesting to evaluate the utility of LUS in the chronic management and serial monitoring of dogs with CVHD under treatment.

Footnotes

[a] 18L7, 10-14 MHz, Toshiba, Monza Brianza.

[b] 9L-D, 2.4-10.0 MHz, GE Healtcare, Milano.

[c] Aplio, Toshiba, Monza Brianza.

[d] Logiq S8, GE Healtcare, Milano.

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Tables

Table 1. Clinical, echocardiographic and radiographic data of all dogs (n = 63).

	Stage B1	Stage B2	Stage C
Number of cases	15	18	30
Male/Female	7/8	11/7	20/10
Age (years)	11.5 (6.0-15.0)	11 (6.0-16.0)	11 (5.0-18.0)
BW (kg)	12 (3.5-40.0)	10 (4.5-27.0)	9 (3.7-37.0)
LA/Ao	1.39 (1.00-1.50)	1.8 (1.60-2.80) [a]	2.3 (1.75-3.68) [a,b]
Emax (m/s)	0.89 (0.66-1.02)	0.98 (0.40-2.04)	1.51 (0.66-2.30) [a,b]
E/A ratio	1.33 (0.75-1.65)	1.10 (0.70-3.00)	2.04 (0.67-4.20) [a,b]
LVIDDn	1.48 (1.25-1.85)	1.87 (1.39-2.34) [a]	2.21 (1.63-2.86) [a,b]
PE (%)	0 (0%)	0 (0%)	20 (66.7%) [a,b]

BW, body weight; LA/Ao, left atrium to aortic root ratio; Emax, peak velocity of E wave of the transmitral flow; E/A, E wave to A wave ratio of the transmitral flow; LVIDDn, normalized left ventricular internal diameter in diastole; PE, pulmonary edema.

Data are expressed as the median (range) or number (percentage).

[a] $P < .05$ as compared to stage B1.

[b] $P < .05$ as compared to stage B2.

Table 2. B-lines of all dogs (n = 63)

	Stage B1 (n = 15)	Stage B2 (n = 18)	Stage C (noPE) (n = 10)	Stage C (PE) (n = 20)
Absent/rare	14 (93,3%)	16 (88,9%)	10 (100%)	2 (10%)
Numerous/confluent	1 (6,7%)	2 (11,1%)	0 (0%)	18 (90%)

noPE, absence of pulmonary edema; PE, pulmonary edema.

Table 3. Diagnostic accuracy of LUS in the detection of pulmonary edema (n = 63)

	No PE (n = 43)	PE (n = 20)
Absent/rare	40 (93%)	2 (10%)
Numerous/confluent	3 (7%)	18 (90%)

Sensitivity 90.0%; specificity 93.0%; positive predictive value 85.7%; negative predictive value 95.2%.

Figure legends

Figure 1. Lung ultrasound images. (A) Absent B-lines (no B-lines). (B) Rare B-lines (≤ 3 B-lines). (C) Numerous B-lines (> 3 B-lines). (D) Confluent B-lines (multiple B-lines blended together).